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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/602,597	06/22/00	DUHL	D 1568.002/200

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EXAMINER	
WEGERT, S	
ART UNIT	**PAPER NUMBER**
1647	13

DATE MAILED: 05/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/602,597	Applicant(s) DUHL ET AL.	
	Examiner Sandra Wegert	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-9, 17-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16* is/are rejected.

7)☒ Claim(s) *10-16* is/are objected to.

8)☒ Claims *1-25* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 6, 9* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement, filed 10/6/00, the Supplemental Information Disclosure Statement, filed 11/20/00, and the Information Disclosure Statement, filed 1/31/01, have been entered into the record.

Applicant's election of Group II, (claims 10-16) and SEQ ID NO: 4 in Paper No. 11 is acknowledged. Claims 1-9 and 17-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The Change of Address Form received May 01, 2001 (Paper 12) has been entered into the record.

Informalities

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "HUMAN CHROMOSOME 16 PLASMOLIPIN-LIKE POLYPEPTIDE."

Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities:

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Appropriate correction is required.

The serial numbers of patent applications recited in the specification must be updated as their status changes; this occurs for example on p. 29, line 13.

Appropriate correction is required.

Claims

Claims 10-16 are objected to because of the following informalities: They recite non-elected inventions.

Appropriate correction is required.

Information Disclosure Statements

The Information Disclosure Statement filed in Paper No. 6 (11/20/00) fails to comply with the provisions of MPEP § 609 because reference 3 is not in English.

Appropriate correction is requested.

Reference number 3 on the Supplemental Information Disclosure Statement PTO 1449 was lined through by the Examiner because: the reference was in a language other than English; the abstract was vague; it could not be determined what the DNA sequences referred to; and no information was given as to the significant sections of the disclosure.

Claim Rejections/Objections

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to a human plasmolipin-like protein, a polypeptide of 216 amino acids that resembles a proteolipid (p. 5, line 17, for example), and is found in the region of chromosome 16 that may code for genes involved in Bardet-Biedl syndrome. However, the specification does not disclose a function for the human plasmolipin-like protein in the context of the cell or organism.

No well-established utility exists for newly isolated complex biological molecules. However, the specification *implies* the following as credible, specific and substantial patentable utilities for the claimed putative polypeptide:

1) For the treatment or prevention of a polypeptide deficiency involved or resulting in Bardet-Biedl syndrome.

2) For the diagnosis of Bardet-Biedl Syndrome or other diseases of the central or peripheral nervous system.

3) For chromosomal localization and/or tissue localization of polynucleotides encoding the claimed plasmolipin-like peptide.

4) For the production of antibodies.

5) To search for physiological activity of the claimed polypeptide or its ligands.

6) To detect ion-transport activity.

Each of these shall be addressed in turn:

1) *For the treatment or prevention of a polypeptide deficiency involved or resulting in Bardet-Biedl syndrome.* This implied utility is specific, however it is neither credible nor substantial. The specification does not disclose a link between Bardet-Biedl Syndrome and a deficiency in the claimed polypeptide. Significant further experimentation would be required of the skilled artisan to identify individuals who would benefit from this sort of procedure, and then to determine a best course of treatment. Therefore, the implied utility is not credible. Additionally, there is no disclosure of whether the polypeptides could be administered, for example, orally or parenterally, nor the dosages needed, nor how to assay for improvement or intolerable levels of side effects, etc. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) *For the diagnosis of Bardet-Biedl Syndrome or other diseases of the central or peripheral nervous system.* Similarly, this asserted utility is credible and specific; however, it is not substantial. The specification does not disclose a link between the claimed polypeptide and

BBS, nor does it disclose *any* diseases associated with altered levels or forms of the plasmolipin-like polypeptide of the claimed invention. Significant further experimentation would be required of the skilled artisan to identify individuals having deficits in the claimed polypeptide, and then correlating that deficit with a clinical syndrome. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) *For chromosomal localization and/or tissue localization of polynucleotides encoding the claimed plasmolipin-like peptide.* This asserted utility may be credible, but it is neither substantial nor specific. Applicant refers, for example, to the use of an RNA hybridization probe for detection of nerve injury, and implies chromosomal localization to detect genes involved in BBS. However, probes and primers can be designed from any polynucleotide sequence; thus the asserted utility is not specific. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) *For the production of antibodies.* This asserted utility is credible and substantial, but not specific. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility.

5) *To search for physiological activity of the claimed polypeptide or its ligands.* Similarly, this asserted utility is credible and substantial. However, it is not specific. Such is performed for any peptide-ligand pair when the physiological role of each is not known. It is the definition of the type of further research that is required for either the claimed polypeptide or the ligand to have patentable utility.

6) *To detect ion-transport activity.* This asserted utility is credible and substantial. However, it is not specific. Such assays can be performed with any channel-forming polypeptide. Hence, the asserted

utility is non-specific. Further, the specification does not disclose that the claimed polypeptide is in fact an actual channel-forming polypeptide. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Claims 10-16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 10-16 are directed to a polypeptide comprising the amino acid sequence of SEQ ID NO: 4. The claims also recite an amino acid sequence at least 95% identical to that of SEQ ID NO: 4, and epitope-bearing portions of SEQ ID NO: 4.

The specification teaches the plasmolipin-like polypeptide as well as epitope fragments of SEQ ID NO: 4. However, the specification does not teach functional or structural characteristics of the plasmolipin-like polypeptide.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in

underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologues must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make biologically active plasmolipin-like protein without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

The specification does not teach the skilled artisan how to use the plasmolipin-like protein for *any* purpose. For example, a disclosure that definitively correlates a particular disease state, such as Bardet-Biedl Syndrome, to an alteration in levels or forms of the plasmolipin-like protein, might enable use of the claimed polypeptide as a diagnostic tool. However, the skilled artisan is not provided with sufficient guidance to use the claimed polypeptides for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed plasmolipin-like protein and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior

art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Furthermore, the specification does not reasonably provide enablement for the polypeptide variants as recited in claim 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The breadth of claim 10 is too large since the specification fails to provide any guidance on how to produce a peptide which is at least 95% identical to SEQ ID NO: 4 and retains the function of SEQ ID NO: 4. Claim 10 refers to any polypeptide, that is "at least 95% identical" to that of SEQ ID NO: 4, without knowledge of the polypeptides that would fall within this range. In other words, no discussion or working examples, in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the claimed polypeptide are disclosed. The instant case claims altering as much as 5% of the polypeptide claimed in SEQ ID NO: 4. The possible effect of changing even one amino acid in a polypeptide can be seen in U.S. Patent 5,350,836 (Kopchick, et al) in which several antagonists of a vertebrate growth hormone differ from the naturally-occurring growth hormone by a single amino acid (column 2, lines 37-48). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second

paragraph of Introduction). These examples and others illustrate that it is not predictable as to which amino acids are necessary to maintain the functional characteristics of a protein.

In summary, the specification does not provide a description of a repeatable process of producing, nor of working examples of making the polypeptides whose amino acid sequences deviate from the disclosed sequence (SEQ ID NO: 4) by as much as 5%. In addition, the predictability of the art is low with regards to the knowledge of what effects altering as much as 5% of the sequence of a polypeptide would have on that polypeptide. For this reason, undue experimentation would be required to determine a structure-function relationship for each possible polypeptide encompassed by the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 10 is directed to an isolated polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2.

The specification teaches a plasmolipin-like polypeptide (SEQ ID NO: 4). However, the specification does not teach functional or structural characteristics of isolated polypeptides. The description of one plasmolipin-like polypeptide species (SEQ ID NO: 4) and one plasmolipin-like polypeptide from residue 2-218 of SEQ ID NO: 4) is not adequate written description of an entire genus of functionally equivalent polypeptides.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The plasmolipin-like polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

Claims 10-16 are rejected for the reasons cited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW

5/9/01

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER